FDA Drug Review in PDUFA IV

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PDUFA IV – Enhanced Funding and Pre-Market Review Process

- **Sound Financial Footing**
  - Significant base increase in user fees plus additional fee revenues for drug safety and improvements in the workload adjustor
  - Eliminated time limits on support of post-market risk management
- **Enhancing Pre-Market Review**
  - Full implementation of Good Review Management Principles and Practices (GRMPs) developed under PDUFA III.
  - More predictable timeframes for FDA-sponsor discussion of proposed labeling and post-marketing study commitments (PMCs)
  - New Guidance Documents to clarify current FDA thinking on specific trial design issues

PDUFA IV – Modernize Post-Market Safety

- Publish drug safety plan
- Identify epidemiology best practices and develop guidance documents
- Expand databases for analysis of new safety signals
- Develop and validate risk management and risk communication tools
- Improve communication and coordination between pre-market review and post-market surveillance functions
- Modernize the process of proprietary name review process

Additional Requirements From FDAAA

- **Title IV – Pediatric Research Equity Act**
- **Title V – Best Pharmaceuticals for Children Act**
- **Title IX – Enhanced Authorities Regarding Post-Market Safety of Drugs**

Title IV: Pediatric Research Equity Act (PREA)

- **Requires sponsors to submit assessments of a drug's claimed indication in relevant pediatric populations – with provisions for deferral and waiver requests.**
- **Establishes Internal Committee for review of assessments, pediatric plans, and requests for deferrals/waivers**
- **Committee responsibilities:**
  - Consult with sponsors on pediatric plans and assessments before approval of an application or supplement or granting a deferral or waiver request
  - Recommend when submissions should receive priority review
  - Perform retrospective analysis of all studies submitted and deferrals/waivers granted since enactment of PREA 2003 for consistency; recommend improvements

Title IV: Pediatric Research Equity Act (PREA)

- **FDA must also track and make publicly available the following:**
  - All medical, pediatric, and clinical pharmacology reviews of pediatric assessments within 210 days of submission
  - Number and types of assessment conducted and the specific drugs and indications studied
  - Number of patients, centers, and countries involved in the studies.
  - Number of deferrals requested, granted, reasons for granting, timelines for completion, and the number completed and pending
  - Number of waivers requested, granted, and reasons for granting
  - Number of pediatric formulations developed, number of pediatric formulations not developed, and the reasons for not developing
  - Labeling changes (including an annual summary) made as a result of pediatric assessments

Title V: Best Pharmaceuticals for Children Act

- **Requires FDA to use the Internal Committee established by PREA**
- **Committee responsibilities:**
  - Review all written requests for pediatric studies (now including preclinical studies) from sponsors before issuance
  - May review pediatric studies to make a recommendation on exclusivity
- **Tracking and posting requirements:**
  - Number and types of studies, drugs studied and their on/off-label indications, number of formulations developed or not, labeling changes
  - All medical, statistical and clinical pharmacology reviews of studies within 210 days of report submission
  - Exclusivity determinations within 30 days of determination
  - Notice of drugs for which a pediatric formulation was found to be safe and effective, but not marketed within 1 year after exclusivity determination is posted.

Title IX: Enhanced Authorities Regarding Post-Market Safety of Drugs

- **Numerous provisions to ensure appropriate management of the entire life cycle of a drug**
  - Pharmacovigilance and Active Surveillance
  - Post-market studies or clinical trials to assess serious safety issues
  - Safety labeling changes
  - Risk Evaluation and Mitigation Strategies (REMS)
    - Medication Guides, Communication Plans, Elements to Assure Safe Use (ETASU), Implementations Systems, Assessments

Implementing FDAAA – major focus since FY2008

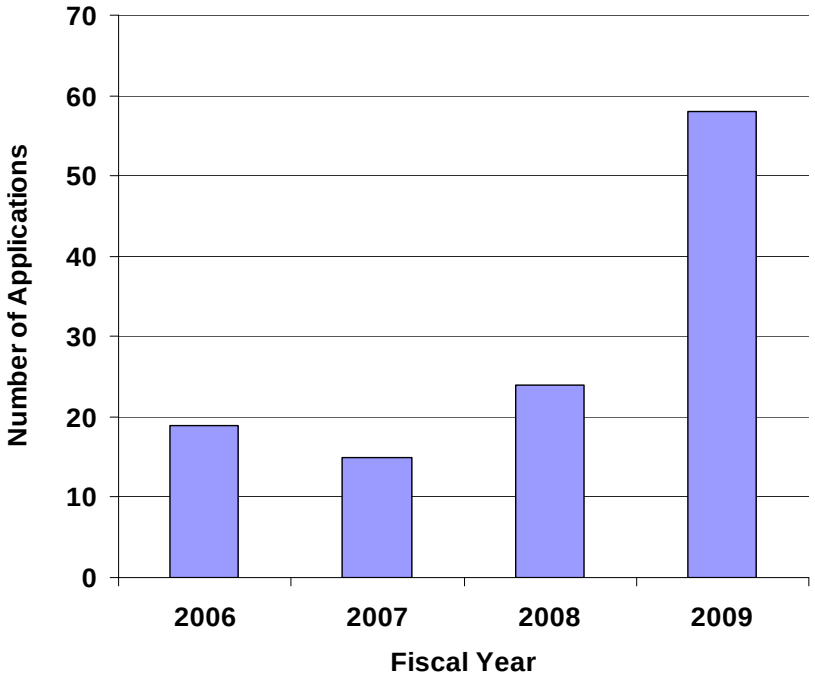
- **Title I – PDUFA**
  - Additional appropriation and user fee resources used to significantly increase drug review and post-marketing safety staffing.
- **Titles IV and V – PREA and BPCA**
  - Pediatric Review Committee established in October 2007
    - 573 recommendations made under PREA involving the review of pediatric assessments, plans, deferrals, and waivers.
    - 42 recommendations made under BPCA involving the review of written requests
    - Completed retrospective analysis of prior studies and deferrals/waivers granted
    - Posted medical, statistical, and clinical pharmacology reviews of pediatric studies
  - By September 30, 2009 – 193 pediatric studies were completed under PREA and BPCA involving 85,475 patients

Implementing FDAAA continued…

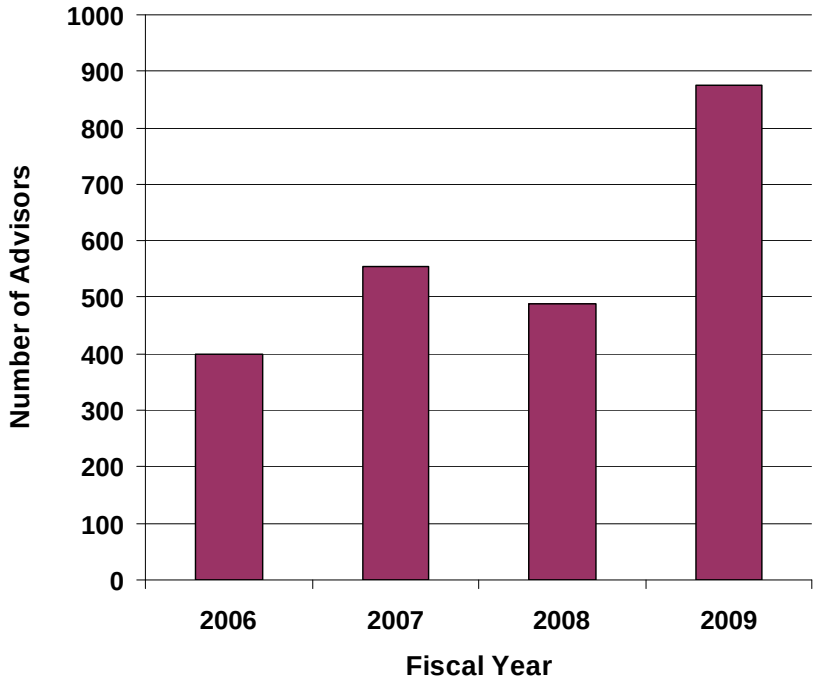
- **Title IX**
  - 108 REMS approved as of March 23, 2010
  - Required over 200 post-marketing studies and clinical trials to assess safety issues as of March 1, 2010
  - Required 32 safety label changes since March 1, 2010
  - Launched public website to list approved REMS and other safety information.
  - Established process for posting action packages in a timely manner
  - Sentinel Initiative – active drug safety surveillance

More NDAs and BLAs are now discussed at Advisory Committee meetings

NDAs / BLAs Requiring An AC Meeting



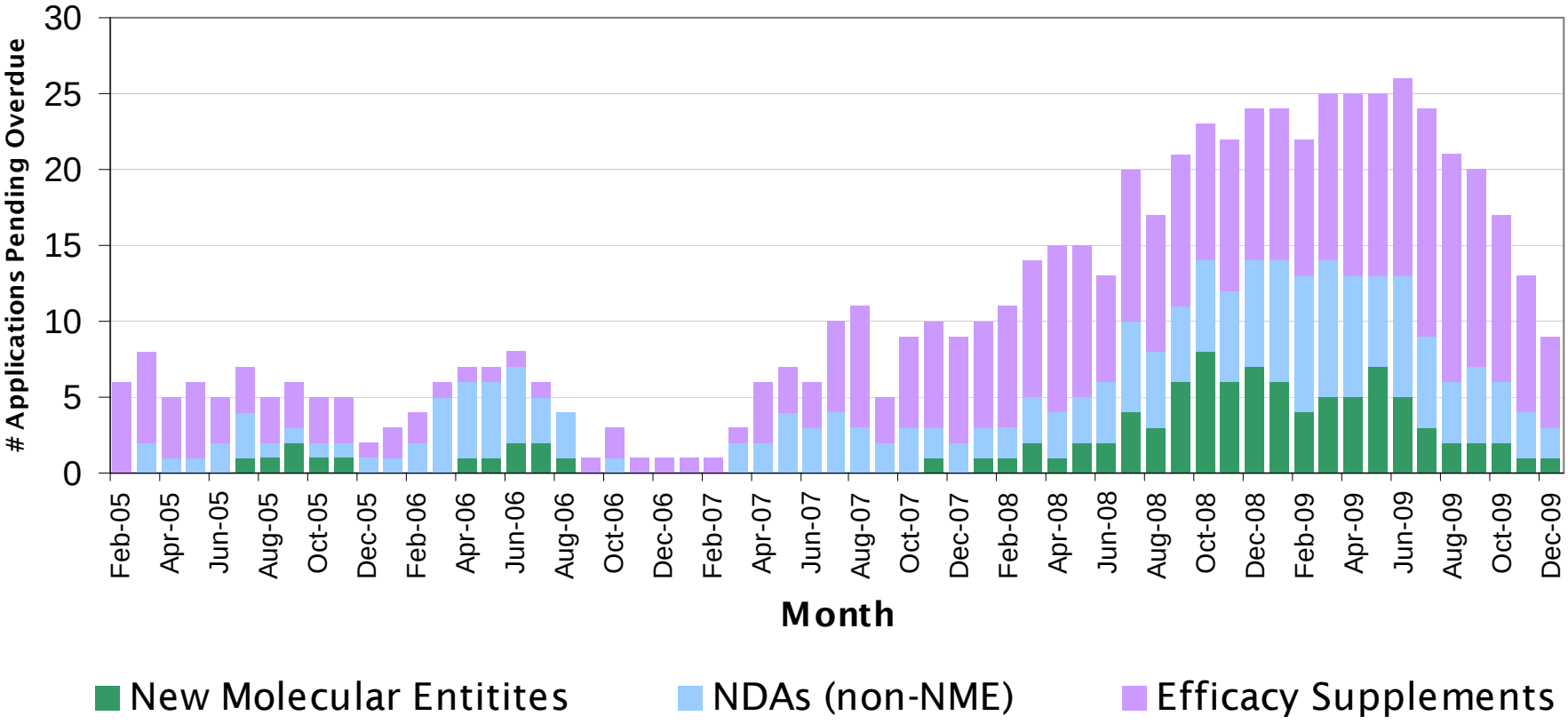
Number of Advisors Screened for AC meetings



PDUFA IV review goal performance reflects near-term impacts of FDAAA

- CDER's recent hiring surge resulted in a decline in the average level of on-board review expertise in PDUFA IV
- New FDAAA requirements (Titles IV, V, and IX) have been inserted into review timeframes agreed to under FDAMA 1997 and were not accounted for in FDA-industry fee negotiations and goals FDA committed to in PDUFA IV.
- PDUFA process and procedural goals (certain meetings) consciously given lower priority in first 12-18 months while new FDAAA provisions being implemented.
  - Review management has refocused pre-FDAAA attention to these

Pending Applications with Overdue PDUFA Goals by Month



Source: CDER Data as of 12-31-2009, excluding biologic license applications (BLAs)

Public Meeting – April 12, 2010

- **Hilton Washington DC/Rockville Executive Meeting Center, 9am-5pm**
- **Purpose – to hear stakeholder views on PDUFA as FDA considers the next PDUFA program**
  - What is your assessment of the overall performance of the PDUFA IV program thus far?
  - What aspects of PDUFA should be retained, changed, or discontinued to further strengthen and improve the program?
- **Reauthorization discussions focus on drug review process, not regulatory policy**